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Public Health Report

Immunogenicity and safety of human papillomavirus (HPV) vaccination in Asian populations from six countries: a meta-analysis

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Abstract

Cervical cancer is a serious public-health problem in Asian countries. Since human papillomavirus (HPV) infection is the main risk factor for cervical cancer, HPV vaccination is considered a promising strategy to prevent cervical cancer. However, comprehensive immunogenicity and safety information for Asian populations is lacking. We searched four electronic databases including PubMed, EMBASE, Cochrane Library, and clinicaltrials.gov. We reviewed selected manuscripts and extracted the pooled relative risk (RR) from immunogenicity and safety information on HPV vaccination among women in Asian countries. We identified two quadrivalent-vaccine studies and eight bivalent-vaccine studies conducted in Asian countries. Analysis across these studies suggested that the HPV vaccines significantly enhanced HPV16- and HPV18-specific antibody among both uninfected (RR 85.69; 95% confidence interval (CI) 31.51–233.04 and 62.77; 95% CI 37.4–105.51) and infected individuals (RR 8.60; 95% CI 6.95–10.64 and RR 8.13; 95% CI 5.96–11.11). Furthermore, HPV vaccination among Asian populations has a favorable safety profile, with only slightly higher risks of local (RR: 1.89; 95% CI 1.65–2.17) and systemic (RR: 1.33; 95% CI 1.18–1.50) adverse events in vaccinated individuals compared with controls. For Asian populations, HPV vaccines enhance the level of HPV16- and HPV18-specific antibodies for both uninfected and infected individuals. Also, the risk of adverse events related to vaccination are acceptable. More data are needed to establish vaccine efficacy with regard to prevention of HPV infection and further outcomes including cervical intraepithelial neoplasia (CIN) and cervical cancer.

Key words: immunogenicity, safety, HPV, HPV vaccination, cervical cancer, Asia

Introduction

Cervical cancer has become a substantial social and economic issue in Asian countries. Indeed, more than half of the worldwide incidence and mortality due to cervical cancer in 2012 occurred in this region (1,2). The number of cases varies widely among Asian countries, with India and China as leading countries. Moreover, it has been shown that, during the last two decades, cervical cancer patients in developing countries have had a lower survival rate compared with those in developed countries (1,3).

The fact that human papillomavirus (HPV) infection, acquired by sexual intercourse, is the main risk factor for cervical cancer has been known since the 1980s (4,5). There are over 100 types of HPV, of which the high-risk types, particularly HPV16, -18, -31, -52 and -58, represent the viruses with oncogenic potential (6–8). Part of the strategies aimed at control of cervical cancer is based on prevention of HPV infection (7). One clinically proven prevention strategy involves HPV vaccination of young girls before they become sexually active (7,9). In 2006, a quadrivalent vaccine (for HPV types 6, 11, 16 and 18) and a bivalent vaccine (for HPV types 16 and 18) were introduced and licensed in over 100 countries worldwide (10–12). In 2013, HPV vaccination was incorporated in the national vaccination programs of almost 40 countries, especially western and developed countries (9).

To support the implementation of prophylactic HPV vaccination, clinical trials have been conducted (13–16). The trials have clearly shown that the HPV vaccines induce high levels of antiviral antibodies (17–21), prevent infection with HPV types contained in the vaccine (13,15), and mitigate the development of premalignant cervical intraepithelial neoplasia (CIN) and cervical cancer (13,16). HPV vaccines are considered safe, with most of the trials showing that the adverse events in the vaccinated groups equal those in comparator groups (17,18).

Notably, the main clinical trials on HPV vaccination have been conducted in the western or developed countries (13,14,16,22) and so far only few Asian countries have participated in HPV vaccine trials. Therefore, specific information on HPV vaccine immunogenicity and safety profiles in Asian populations is scarcely available. Extrapolation of results of vaccine trials from western to Asian countries is questionable since trials outcome, for example vaccine efficacy, might be different as it possibly caused by several variables, including race as well as social and behavioral factors (23,24). Therefore, it is important to obtain specific estimations of the characteristics of HPV vaccination in Asian populations, especially with respect to immunogenicity, efficacy and safety. In this study, we investigate the immunogenicity and safety profiles of HPV vaccines among both uninfected and infected populations in Asian countries by systematically reviewing available scientific evidence and performing a meta-analysis of randomized controlled trials.

Methods

Databases and search methods

We systematically searched for randomized controlled clinical trials (RCT) on HPV vaccination among women in Asian countries from four electronic databases (PubMed, EMBASE, Cochrane Library and clinicaltrials.gov). We focused on studies that evaluated the immunogenicity and safety profiles of the vaccination.

On PubMed, we combined the MeSH term and text word from each of the following keywords: ‘Human Papillomavirus’ (hvp OR human papillomavirus OR hpv 16 OR hpv 18) AND ‘HPV vaccine’ (papillomavirus vaccine OR vaccine) AND ‘Asia’. We also used the

same keywords in EMBASE using *exp* (explosion search), *ab* (abstract), and *ti* (article title) commands. Moreover, we searched ‘hpv vaccine’ in the Cochrane Library to detect all clinical trials on HPV vaccines and screened the studies manually. In addition, we applied the search term ‘hpv’ in clinicaltrials.gov. Only studies conducted in Asia were included.

Data collection and analysis

We included all RCTs performed in Asian populations that provided immunogenicity and safety data of HPV vaccination as outcomes. We only included studies providing the required information for each outcome. Databases as off 21 November 2014 were used, and we only included papers written in English. Two reviewers (D.S. and J.L.) assessed the studies independently and any disagreement was discussed and solved with a third reviewer (MJP). Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (25), we extracted the following data: authors, year published, country, protocol number, funding source, subject gender and age, active component of the vaccine, vaccine adjuvant, component of the comparator, total sample on both intervention and comparator groups, administration schedule, frequency of immunogenicity test, immunogenicity assessment method, the cut-off point for HPV type 16 and 18 analysis, length of the trial, and the method used for analysis.

The risk of biases from all studies was assessed based on The Cochrane Collaboration’s tool for assessing risk of bias in randomized trials (26). We used the categorization ‘low’, ‘high’, and ‘unclear’ risk of bias to assess this aspect. Irrespective of bias risk, all screened and selected eligible studies were included in the review and meta-analysis.

To perform the meta-analysis, we extracted immunogenicity (seroconversion) and safety (local and systemic adverse events) data from all selected papers. Seroconversion was mainly estimated from participants who were shown to be seronegative to HPV at the initial phase of the studies. In addition, we also included study populations with seropositive results at the beginning of the study to investigate the influence of HPV vaccination for infected individuals. Local adverse events included pain, redness and swelling at the site of injection, while systemic adverse events comprise arthralgia, fatigue, fever, gastrointestinal symptoms, headache and myalgia.

Relative risks (RR) were calculated from the number of events including seroconversion and adverse events in vaccinated groups compared with control groups using a random-effects models to obtain the vaccine immunogenicity and safety profile (27). In order to deal with heterogeneity introduced by the differences in the methods and sample characteristics, we performed a heterogeneity test by quantifying the I^2 score based on Cochrane Q test results (28). This method presents a quantitative value of heterogeneity ranging from 0% to 100% and according to Cochrane recommendation, I^2 of 50% or higher are considered to have a substantial heterogeneity (29) and sensitivity analysis was performed. The uncertainty of each result is presented in terms of 95% confidence intervals (CI). In addition, to analyze the impact of variables on the outcome, we performed subgroup analyses on immunogenicity profiles based on immunoassay and vaccine type. Meta-analysis was performed using RevMan 5.3 for Windows.

Results

Article selection process

We identified 465, 454, 84 and 82 articles from PubMed, EMBASE, Cochrane Library and Clinicaltrial.gov, respectively. From these,

21 duplicated articles were removed and 1064 articles were screened based on title and abstract. Most of these articles did not meet the inclusion criteria. Finally, 19 full-text articles were assessed for eligibility, from which nine articles were excluded for reasons elaborated in Fig. 1. Finally, 10 articles were considered (30–39) in the systematic review and meta-analysis.

Study characteristics

Included studies are listed in Table 1. Clinical trials on HPV vaccination in Asia were performed in six different countries (Korea, Japan, India, China, Bangladesh and Malaysia) and funded by three different companies: Merck, GlaxoSmithKline (GSK), and Grameenphone (the first two in pharmaceuticals, the latter in telecommunication). Most of the studies ($N = 7$) provided their clinical trial registration numbers (31–35,38,39). In addition, almost all studies ($N = 9$) included only women (30–36,38,39). In general, the age of participants in the studies varied considerably from 9 to 45 years.

Both HPV vaccines were investigated in the 10 different trials: the bivalent vaccine from GSK (containing HPV types 16 and 18) in eight trials (31–36,38,39) and the quadrivalent vaccine from Merck (containing HPV types 6, 11, 16 and 18) in two trials (30,37). The majority of the studies included placebo as the comparator (30,33–39); two studies on the bivalent vaccine used the Hepatitis A virus vaccine as comparator (31,32). The number of persons included in most of the studies was less than 1000, but one study in China included 6051 persons, and investigated not only immunogenicity and safety of the vaccine but also vaccine efficacy on the prevention of 6-months persistence of infection and CIN associated with HPV16 and/or HPV18 infection (39).

Studies with the bivalent vaccine implemented administration schedules of 0, 1 and 6 months in the trial (31–36,38,39), while studies with the quadrivalent vaccine implemented an administration schedule of 0, 2 and 6 (30,37). Although almost all studies performed immunogenicity testing at 7 months in the trial, there was one study that performed more extensive immunogenicity testing at

7, 12, 14, 36 and 48 months, with the primary endpoint of the latter study being assessment of vaccine efficacy with respect to prevention of 6-months persistent infection and/or histopathologically confirmed CIN associated with HPV16 and/or HPV18 (39).

Specific cut-off points were implemented to determine the status of HPV-specific antibodies. In the bivalent-vaccine studies, the cut-off points were 8 EU/mL and 7 EU/mL for antibodies against HPV16 and -18, respectively (31–35,38,39). The studies involving the quadrivalent vaccine applied competitive immunoassay, using 20 mMU/mL (milli-Merck unit/milliLiter) and 24 mMU/mL as cut-off points for antibodies against HPV16 and HPV18, respectively (30,37). One study in Bangladesh involving the bivalent vaccine used ELISA and calculated the cut-off point based on the mean optical density of 450 nm to determine the presence of HPV-specific antibodies (36). The study periods in the studies ranged from 7 to 31 months. All studies were performed according to the total vaccinated cohort (intention-to-treat) method or per-protocol analysis for immunogenicity and safety, respectively.

The risk of bias assessment

Although all studies claimed that exact randomized controlled procedures were performed, only six studies described how these random sequences were generated (32–35,38,39) and only five studies explained in detail how the allocation process of each participant in either vaccinated or control group was blinded (33–35,38,39). Most of the studies ($N = 6$) did not explain how participants and researchers were blinded (31,33–36,38) or how the outcome assessment process was blinded ($N = 9$) (30,31,33–39). One study presented incomplete outcome results (36) and there were four studies with a unclear risk of bias on selective reporting (Fig. 2).

Immunogenicity profile

As mentioned, the participants' HPV16- and HPV18-specific antibody profiles were determined using specific cut-off points based on either ELISA for the bivalent vaccine or competitive immunoassay

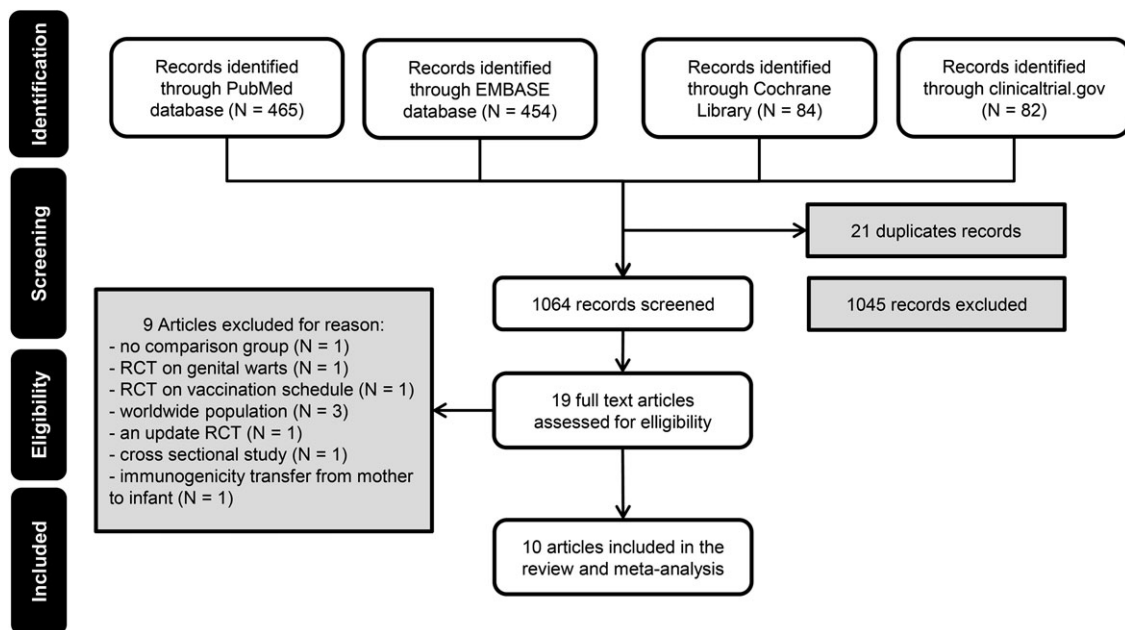


Figure 1. Flow diagram for selection of studies included in the study.

Table 1. Characteristics of studies included in the review

Authors	Kang, 2007 (30)	Konno, 2009 (31)	Kim, 2010 (32)	Bhatla, 2010 (33)	Ngan, 2010 (34)	Kim, 2011 (35)	Khatun, 2012 (36)	Li, 2012 (37)	Lim, 2013 (38)	Zhu, 2014 (39)
Country	Korea	Japan	Korea	India	China (Hong Kong)	Korean	Bangladesh	China	Malaysia	China
Protocol number	–	NCT00316693	NCT00290277	NCT00344032	NCT00306241	NCT00485732	–	–	NCT00345878	NCT00779766
Funding source	Merck & Co Inc	GSK	GSK	GSK	GSK	GSK	Grameenphone Ltd	Merck & Co Inc	GSK	GSK
Gender	Female	Female	Female	Female	Female	Female	Female	Female and male	Female	Female
Patient age	9–23	20–25	10–14	18–35	18–35	15–25	9–13	9–45	18–35	18–25
<i>Intervention & comparator</i>										
Vaccine component	HPV 16, 18, 6, and 11	HPV 16 and 18	HPV 16 and 18	HPV 16 and 18	HPV 16 and 18	HPV 16 and 18	HPV 16 and 18	HPV 16, 18, 6, and 11	HPV 16 and 18	HPV 16 and 18
VLP amount (µg)	20/40/40/20	20	20	NS	20	20	20	20/40/40/20	20	20
Vaccine adjuvant	AAHS	AS04	AS04	AS04	AS04	AS04	AS04	AAHS	AS04	AS04
Comparator	Placebo	HAV	HAV	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Comparator adjuvant	AAHS	NS	NS	Al(OH) ₃	Al(OH) ₃	Al(OH) ₃	Al(OH) ₃	AAHS	Al(OH) ₃	Al(OH) ₃
Total sample intervention	117	516	160	176	150	149	50	302	135	3026
Included in safety testing	117	516	126	167	145	140	50	302	131	2987
Included in immunogenicity testing	108	413	120	153	106	137	49	287	126	396
Total sample comparator	59	519	161	178	150	76	17	298	136	3025
Included in safety testing	59	519	132	170	145	68	17	298	131	2985
Included in immunogenicity testing	58	393	128	159	101	67	NS	282	129	399
<i>Clinical protocol</i>										
Administration schedule (months)	0, 2, 6	0, 1, 6	0, 1, 6	0, 1, 6	0, 1, 6	0, 1, 6	0, 1, 6	0, 2, 6	0, 1, 6	0, 1, 6
Frequency of immunogenicity testing (month)	0, 7	0, 6, 7	0, 7	0, 7	0, 7	0, 7	0, 7	0, 7	0, 7	0, 7, 12, 24, 36, 48
Immunogenicity assessment method	Competitive immunoassay	ELISA	ELISA	ELISA	ELISA	ELISA	ELISA	Competitive immunoassay	ELISA	ELISA
Cut-off point (HPV type 16/18)	20/24 mMU/mL	8/7 EU/mL	8/7 EU/mL	8/7 EU/mL	8/7 EU/mL	8/7 EU/mL	450 nm	20/24 mMU/mL	8/7 EU/mL	8/7 EU/mL
Length of trial (months)	8	7	10	18	16	10	17	7	16	31
<i>Population for analysis</i>										
Immunogenicity	ATP cohort	ATP cohort	ATP cohort	ATP cohort	ATP cohort	ATP cohort	ATP cohort	ATP cohort	ATP cohort	ATP cohort
Safety	TVC	TVC	TVC	TVC	TVC	TVC	TVC	TVC	TVC	TVC

GSK, GlaxoSmithKline; HPV, human papillomavirus; AAHS, amorphous aluminum hydroxyphosphate sulfate; AS04, aluminum hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A; HAV, Hepatitis A virus; Al(OH)₃, aluminum hydroxide; ELISA, enzyme-linked immunosorbent assay; mMU/mL, mili-Merck unit/miliLiter; EU/mL, ELISA Unit/milliliter; ATP, according to protocol; TVC, total vaccinated cohort

for the quadrivalent vaccine. Furthermore, seroconversion was calculated by comparing the patients' status at the start of the study (month 0) and 1 month after the last dose (month 7), and pooled RR of seroconversion among both vaccinated and control groups was analyzed using a random-effects model. We also describe the seroconversion according to the type of vaccine (bivalent or quadrivalent). In addition, there were significant differences on Geometric Mean Titer (GMT) between vaccinated and comparator groups with mean differences of 11 866.60 (95% CI 8 443.93–15 289.25) and 5724.71 (95% CI 3685.09–7764.33) for HPV-16 and HPV-18, respectively (data not shown).

There was a higher number of seroconversions on HPV16-specific antibodies in the vaccinated groups compared with the control groups, and the difference was statistically significant (RR at 62.52; 95% CI 16.29–239.96). However, the heterogeneity among the pooled studies was moderately high ($I^2 = 88\%$; P value < 0.001). This heterogeneity was remarkably caused by a study from India as it has a narrow confidence interval and its mean estimate was far from the ones estimated from the other studies included in the meta-

analysis. A sensitivity analysis, excluding a study from India, showed that the difference was consistently high (RR at 75.54; 95% CI 30.76–185.46) and the heterogeneity was moderately low ($I^2 = 47\%$; P value < 0.07) (data not shown). With respect to vaccine type, the pooled RR on seroconversion for the 7 RCTs using the bivalent vaccine and 2 RCTs using quadrivalent was 44.86 (95% CI 11.90–169.15) and 252.65 (95% CI 35.77–1784.59), respectively. The influence of each individual study on the pooled immunogenicity was comparable, with equal weights for each study lying between 9% and 13.6% (Fig. 3).

A positive influence from HPV vaccination with regard to HPV18-specific immunogenicity (6 RCTs; 2472 participants) was observed, with a pooled RR of 50.14 (95% CI 31.17–80.68). Moreover, there was no significant heterogeneity among the studies ($I^2 = 0.00\%$; P value = 0.88). Six trials were included in the analysis of the bivalent vaccine's immunogenicity on HPV18, with a pooled RR at 43.22 (95% CI 25.35–73.68), illustrating a significant increase in seroconversion due to vaccination. As expected, the quadrivalent vaccine also demonstrated a statistically significant increase in the

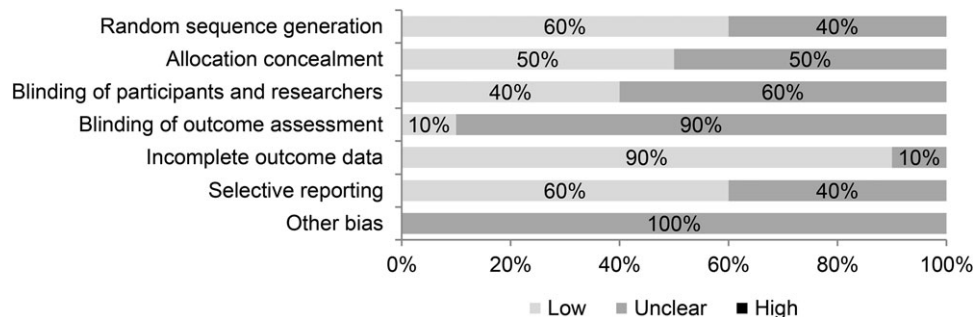


Figure 2. Risk of bias: author's judgment about each risk of bias item presented as percentages across all included studies.

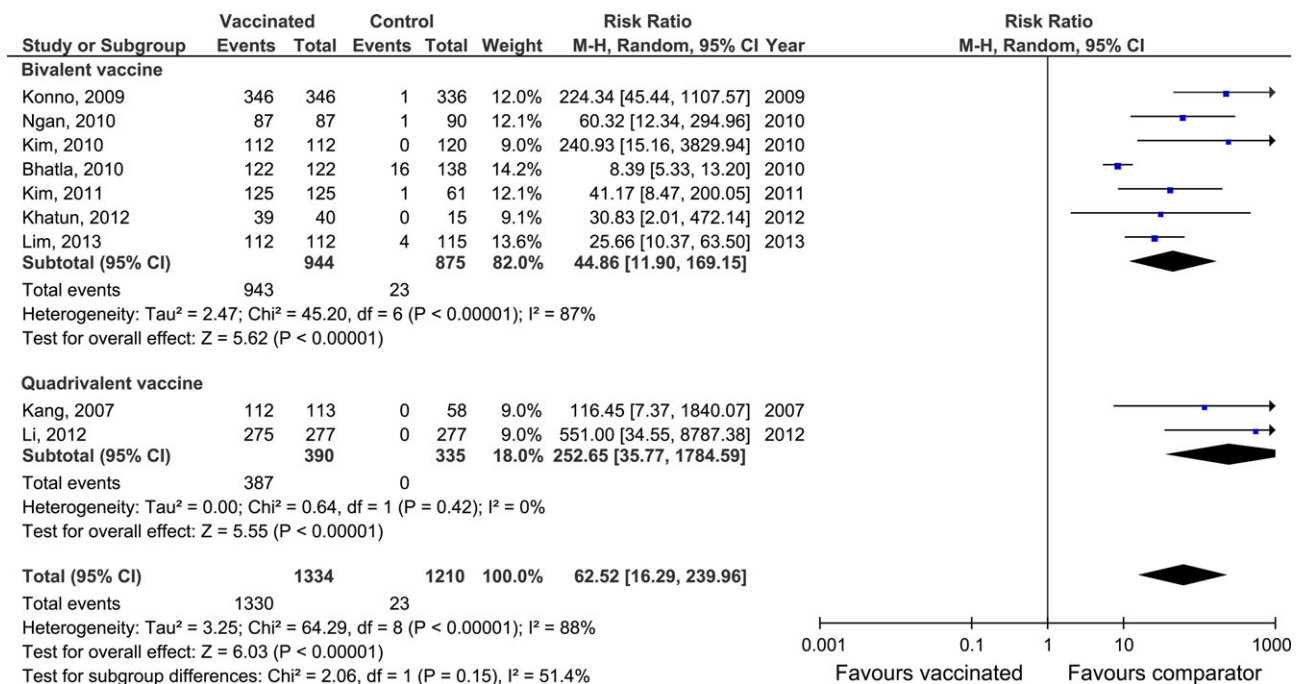


Figure 3. Comparison of human papillomavirus (HPV) vaccines versus control regarding HPV16-specific antibody conversion rate in HPV-uninfected Asian populations.

level of HPV18-specific antibodies (2 RCTs; 737 participants), with a pooled RR at 96.04 (95% CI 33.87–272.34). The pooled result on the vaccine's immunogenicity for HPV18 was strongly influenced by a single study from Japan with by far the largest number of events compared with the other studies (Fig. 4).

Furthermore, our pooled analysis showed that HPV vaccines significantly stimulated HPV16-specific (RR 8.60; 95% CI 6.95–10.64) and HPV18-specific (RR at 8.13; 95% CI 5.96–11.11) antibody levels in combined populations, both infected and uninfected individuals at the start of the study (Fig. 5). The clinical trial results on the

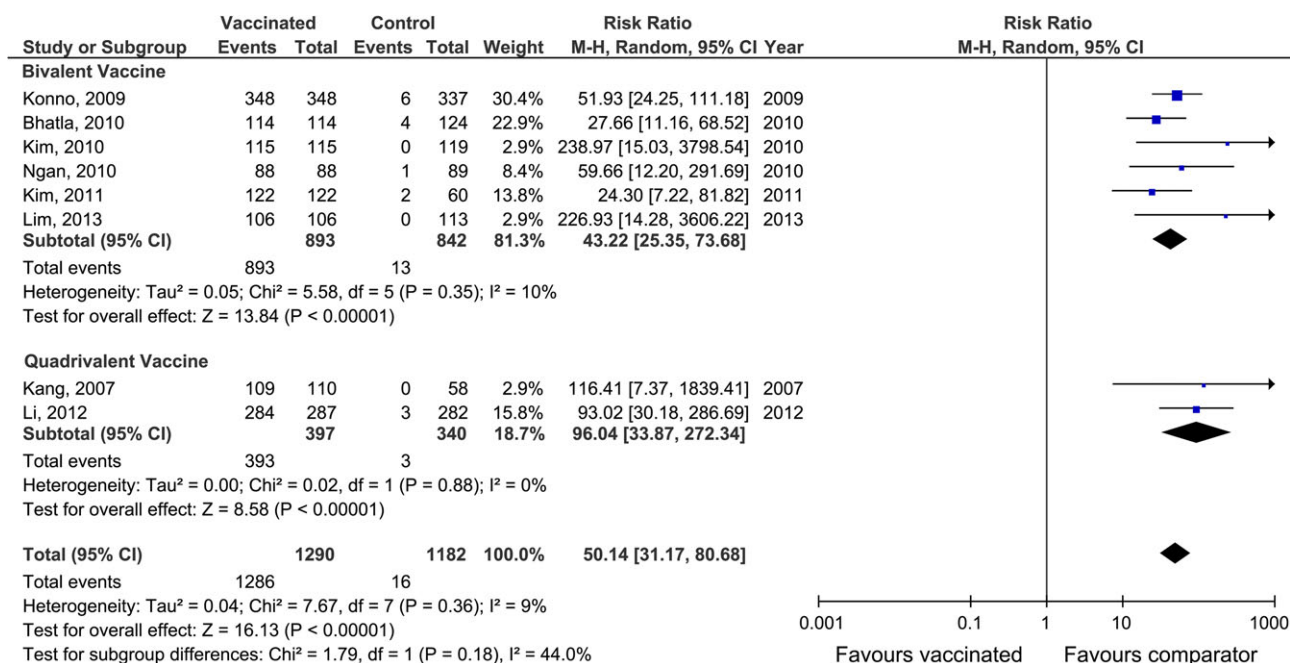


Figure 4. Comparison of HPV vaccines versus control regarding HPV18-specific antibody conversion rate in HPV-uninfected Asian populations.

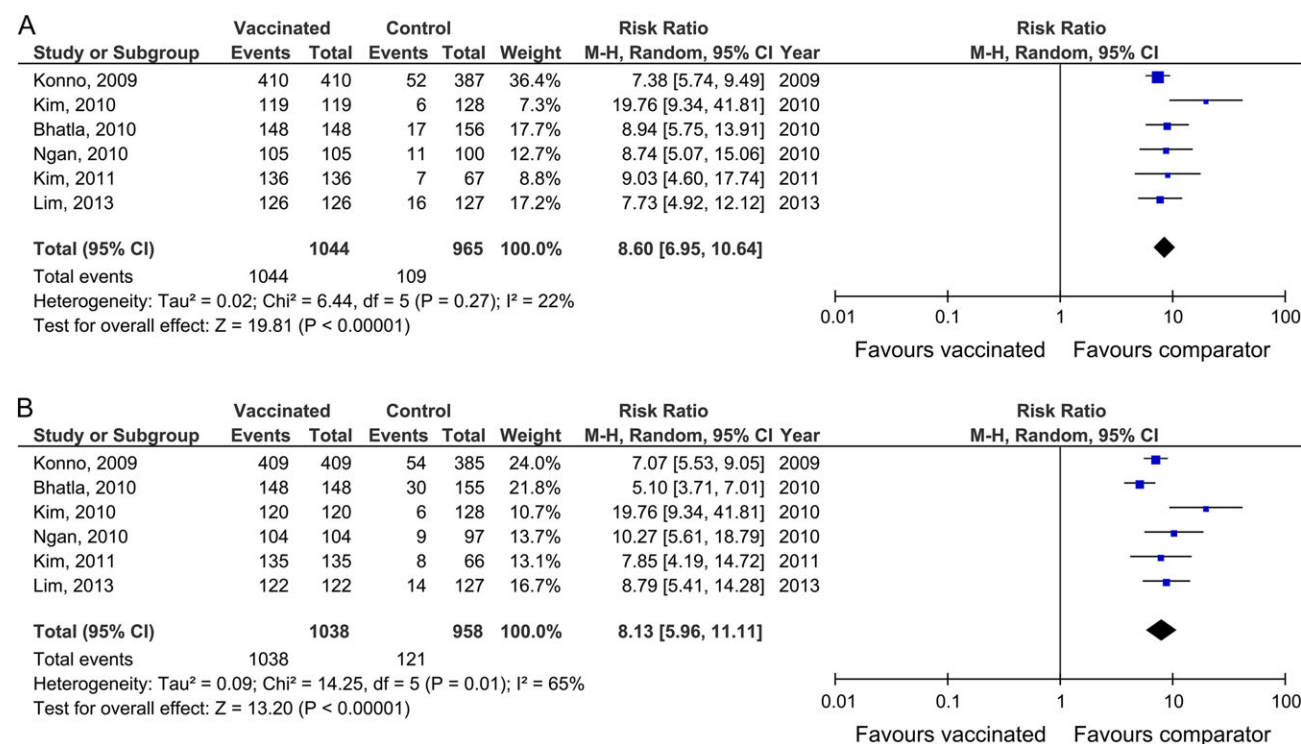


Figure 5. Comparison of HPV vaccines versus control regarding HPV16-specific (A) and HPV18-specific (B) antibody conversion rate in combined HPV-infected and uninfected Asian populations.

vaccine's immunogenicity for HPV16 ($I^2 = 22\%$; P value = 0.27) were considerably less heterogenic compared with those for HPV18 ($I^2 = 65\%$; P value = 0.01). Again, the study from Japan was of considerable influence.

Safety of the vaccines

Risks of various adverse events, including local and systemic reactions potentially related to the vaccines or the injection procedure, were calculated from both vaccinated and control groups. Local adverse events were described as pain, redness and swelling, while systemic adverse events included arthralgia, fatigue, fever, gastrointestinal symptoms, headache and myalgia.

In most studies, local adverse events were reported between 5 and 7 days after each vaccination for both vaccinated and control groups. The risk of pain after injection in vaccinated groups was higher than control groups (RR at 1.6; 95% CI 1.36–1.88). However, the heterogeneity of the results among studies was significant ($I^2 = 86.53$; P value < 0.0001). Among vaccinated individuals,

the risk of swelling at the site of injection was slightly higher (RR at 2.75; 95% CI 2.23–3.38) than the risk of redness (RR at 1.81; 95% CI 1.53–2.16). Moreover, the heterogeneity of the results on the risk of swelling among the different studies was low ($I^2 = 34$; P value: 0.18). In total, the risk of local adverse events experienced by vaccinated groups was higher than control groups (RR at 1.89; 95% CI 1.65–2.17) (Fig. 6).

Systemic adverse events were generally recorded until 30 days after vaccination. The risks of arthralgia (RR at 1.94; 95% CI 1.55–2.43) and myalgia (RR at 1.84; 95% CI 1.61–2.10) were higher in the vaccinated groups than in the control groups. Four types of systemic adverse events had similar risks between vaccinated and control groups (fatigue with an RR of 1.17 and 95% CI of 0.99–1.40, fever with an RR of 1.18 and 95% CI of 0.95–1.48, GI symptoms with an RR of 1.12 and 95% CI of 0.78–1.62, and headache with an RR of 1.09 and 95% CI of 0.90–1.31). Finally, the risk of overall systemic adverse events in the vaccinated groups was slightly higher than in the controls (RR at 1.33; 95% CI 1.18–1.50) (Fig. 7).

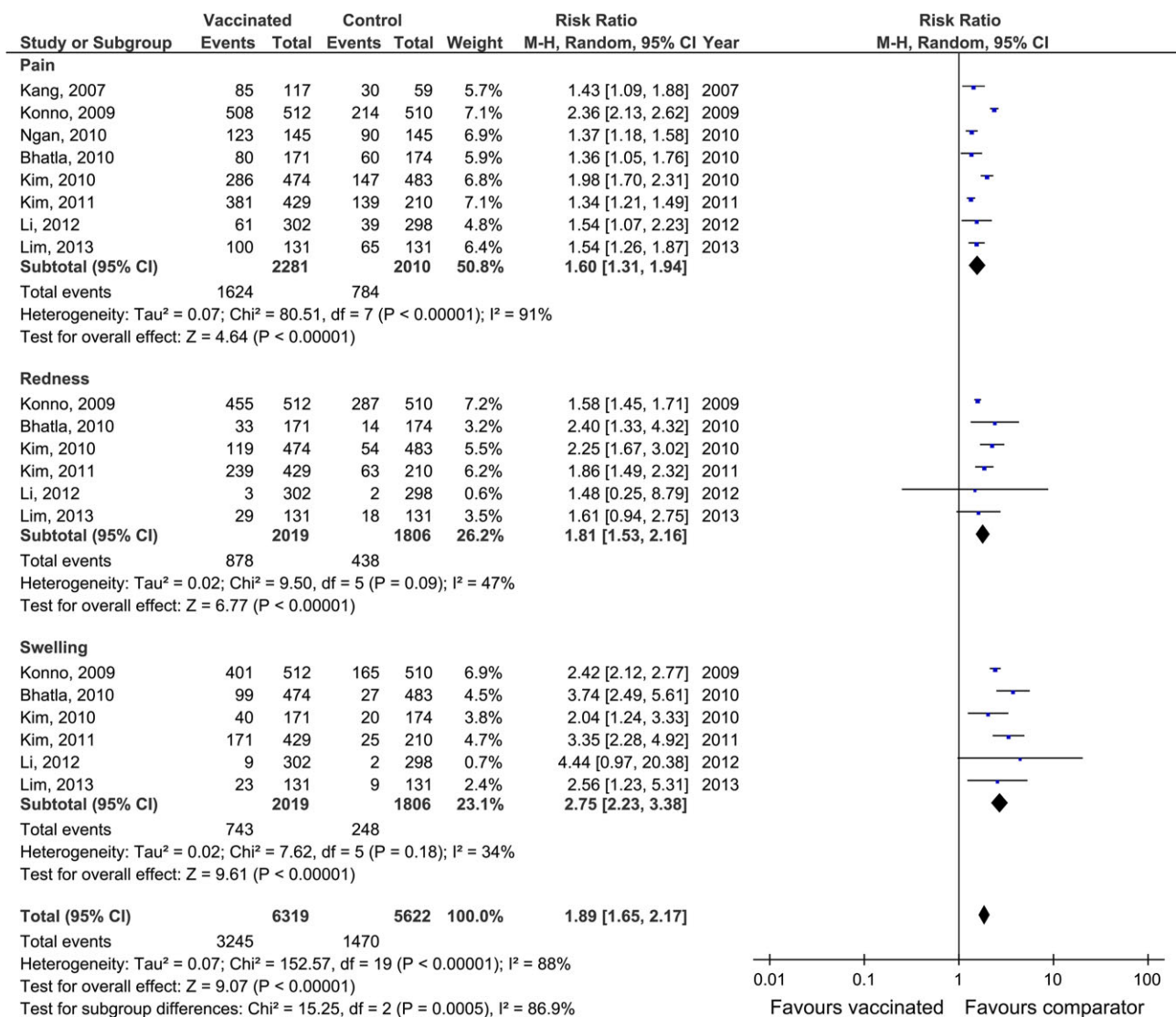


Figure 6. The risk of local adverse events.

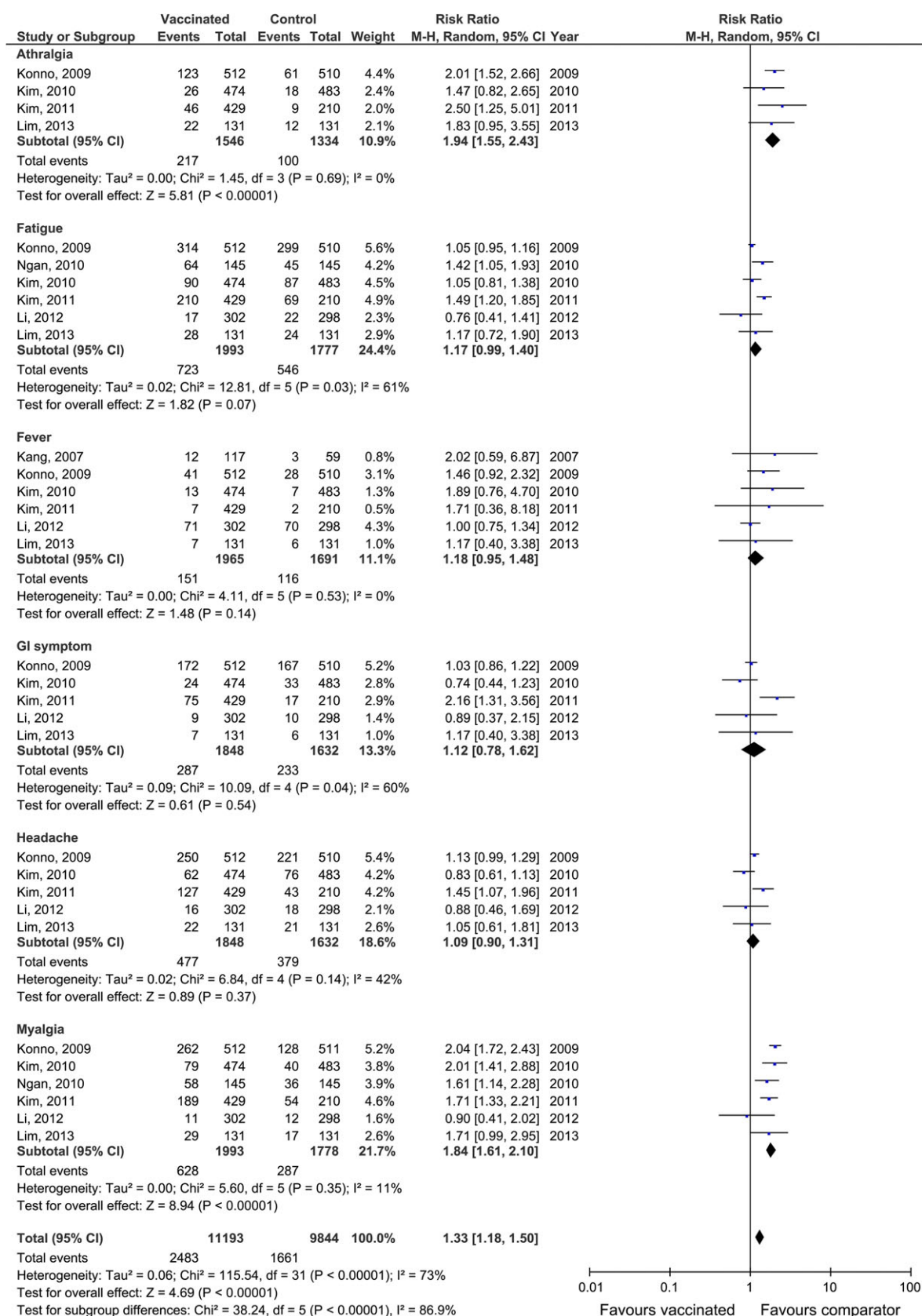


Figure 7. The risk of systemic adverse events.

Discussion

Clinical trials, including vaccine-related trials, are often performed in developed countries such as European countries, the USA, Australia and Japan (13,14,22,40), since in those countries the infrastructure and regulations are well established. However, developing countries, including Asian countries, which are severely affected by infectious diseases and therefore could benefit substantially from vaccination, cannot simply adopt the trial results from developed countries, as the outcomes from vaccination may be different. For example, a study on rotavirus vaccination showed differences in the performance of the vaccine, in particular with regard to its protective efficacy, between developed and developing countries (24). Therefore, evidence from specific populations, including Asian populations, such as that generated by the current meta-analysis on HPV vaccination in various Asian countries, reflects important information for the region.

Currently available prophylactic HPV vaccines offer protection against cervical cancer and premalignant cervical disease by stimulating the induction of HPV16- and HPV18-specific antibodies. This meta-analysis shows that these HPV vaccines are highly immunogenic, in terms of induction of HPV16- and HPV18-specific antibodies, in Asian populations. In addition, the aggregate value of the GMT also demonstrated that HPV vaccines were highly immunogenic in terms of HPV-specific antibody stimulation. The current findings on the vaccines' immunogenicity are perfectly comparable to the results of numerous studies conducted in western countries, including the US, European countries, Australia (41–43), or other regions such as Latin America (40) and Africa (44). The studies evaluated in this meta-analysis involved similar research methods compared with earlier studies, including sample characteristics, vaccine types, dosing, and administration schedules. Thus, the similarity in outcomes underlines the robustness of the vaccines and indicates that there is little influence of ethnicity on the performance of the vaccines.

Not only primary HPV infection, but also recurrent infections may be the cause of the development of HPV-related cancer (45). This recurrence shows that the antibodies induced by a primary infection may not always be sufficient to prevent subsequent infection. Therefore, the application of HPV vaccination of populations that have already undergone earlier HPV infection and have recovered from this infection, potentially provides benefits by preventing possible recurrent infection and subsequent cervical cancer in the future. Our analysis on both infected and uninfected populations showed that HPV vaccines cause an increase HPV-specific antibody levels, also in populations that have undergone a prior HPV infection. Furthermore, our findings are consistent with several studies on the vaccines' immunogenicity from other regions in the world, which also included both uninfected and infected individuals in their study populations (42–44).

According to our meta-analysis, the safety profiles of HPV vaccines were acceptable for Asian populations, with the risk difference of adverse events for vaccinated and control groups are low. Yet, some local (injection site related) and systemic reactions (arthralgia and myalgia) were more common in the vaccinated groups, which is consistent with previously reported findings from several other regions (41–44,46). Nevertheless, to obtain a complete description on HPV vaccines' safety in Asian populations, further studies should be performed, including long term effects, adjuvant-based vaccination and the potential risks of vaccination in pregnancy.

There are several limitations to the evidence presented in this study. The most important concerns that subgroup analysis on the participant's age were not possible since there were only two studies

in young girls' populations and they did not provide sufficient information on immunogenicity and safety of the vaccines. Yet, the study from Schwarz et al. (18) – enrolling 10–14-year-old girls – and several studies concerning older women showed that HPV vaccine apparently induced high anti-HPV antibody levels up to 6 years post-vaccination for both age groups. These data underline that both young girls and older women may benefit from prophylactic HPV vaccination, as discussed above.

Heterogeneity in results was observed on the vaccines' immunogenicity for HPV16 in uninfected individuals. According to the sensitivity analysis, this heterogeneity might be caused by differences related to the trial sites, as most other characteristics of the studies included in our analysis were comparable and the weight of each study was equal. Notably, pooled immunogenicity of HPV16 in uninfected individuals was strongly influenced by one study from India with the highest numbers of seroconversions in the control group. Notably, the incidence of HPV infection in India, particularly that of HPV16, is high compared with other Asian countries (2,47,48). Exclusion of this study from the analysis resulted in a substantially lower heterogeneity in the results with respect to immunogenicity of the HPV16 component in uninfected individuals.

Publication bias could possibly be caused by the exclusion of unpublished studies in the meta-analysis (49,50). We used standard methods to analyze potential publication bias using funnel plots. With respect to the local and systemic adverse events of HPV vaccines, the funnel plots indicated the absence of publication bias (data not shown). We indeed tried to reduce the risk of publication bias by including hand search of literature, inspection of the reference list (snowballing) and searches in databases for ongoing research. Also, as conflicting results on immunogenicity profiles of HPV vaccines are rare, we feel that the results of our analysis can be considered to be valid.

Theoretically, the use of DerSimonian and Laird (DL) generic random-effects model, which is commonly provided in Meta-Analysis software, could possibly lead to deficiencies in generating pooled risk ratio in meta-analyses for relatively low absolute numbers of cases, as is the case in our analysis. However, Shuster and Walker (2014) who reviewed the possible solution for this concern, found that the majority of meta-analysis studies published in JAMA provides similar results when it were analyzed with both DL or Shister, Guo and Skylar (SGS) methods, with the latter being considered as the possible solution for low-event rates in meta-analysis. Moreover, the confidence interval generated by these methods were also considerably similar (51).

Our results provide important information in terms of the immunogenicity and safety of prophylactic HPV vaccines in Asian populations. The observation that HPV vaccines are highly immunogenic and safe for Asian population is consistent with the outcome of HPV vaccination studies from other regions and underlines the robustness of the performance of these vaccines. Since the correlation between HPV16 or HPV18 infection and the development of cervical cancer is well established, implementation of HPV vaccination as a cervical cancer prevention strategy in Asian countries seems indicated and justified. Yet, individual country-specific information, especially cost-effectiveness information (52,53), will obviously be required for ultimate decision making with regard to implementation of HPV vaccination in specific Asian countries.

Although promising results on preventing HPV infection, CIN and cervical cancer were generated by clinical trials on prophylactic HPV vaccination in several regions in the world (11,54,55), cervical cancer incidence and mortality in the Asian region remains high, in

the absence of broad implementation of the vaccines so far (1,2,56). Only a few countries in Asian regions, including Nepal, and Malaysia, provide HPV vaccines as national policies (57). This might be caused by several issues, such as lack of Asian-context-specific evidence on the efficacy of HPV vaccination, socioeconomic barriers, and most importantly, scarce national budgets which hamper implementation of HPV vaccination in most of Asian countries (58–60). However, each year of delay means that an entire birth cohort in a country will miss the opportunity of being offered cervical cancer prevention by HPV vaccination (61). Broader incorporation of HPV vaccination into national policies could produce significant benefits with regard to the burden of cervical cancer. Indeed, factors that contribute to the delay in implementation of prophylactic HPV vaccination in Asian countries should be addressed comprehensively.

One important aspect concerns the evidence for efficacy and safety in the specific Asian context. Notably, as shown here, vaccine immunogenicity and safety studies from Asian countries show comparable outcomes to studies in other regions, including those in developed countries. For overcoming potential barriers in the area of socioeconomics, including acceptance, adherence (62,63), education and promotion of HPV-related cancer prevention should be further substantiated. Direct promotion by health-care professionals is considered as the optimal strategy (63). In the end, country-specific information, such as cost-effectiveness studies or budget impact analysis of HPV vaccination should be performed to ensure allocation of funding toward optimal preventive strategies against HPV-related cancer, especially when budgets are limited (64,65).

The results of the present meta-analysis demonstrate that immunization with the currently available bivalent and quadrivalent HPV vaccines is immunogenic and safe among Asian populations, justifying potential incorporation of HPV vaccination in national cervical-cancer prevention and immunization programs in the region. Important recent developments in the area of HPV vaccination include the introduction of a nonavalent vaccine, which covers more oncogenic HPV types than the current vaccines and potential dose reductions. A nonavalent HPV vaccine has been approved recently by the FDA in the US and by the European EMA (8,66). Introduction of this vaccine will likely result in substantial price reductions of the current vaccines, which nonetheless prevent the large majority of cervical cancer cases. This may remove an important barrier for implementation of HPV vaccination in many Asian countries. In addition, vaccine dose reductions has been suggested by several studies from both Asian (67) and other regions (68). This reduction offers several potential advantages including higher adherence, less budget for its implementation and potentially further decreased risks for any adverse effects. A further important factor in relation to implementation of HPV vaccination involves the issue of co-infection with HIV, the latter worsening the prognosis of HPV infection with enhanced progression to CIN and cervical cancer. Accelerated implementation of prophylactic HPV vaccination would appear to be warranted under these conditions.

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Conflict of interest statement

None declared.

References

- Moore MA, Tajima K. Cervical cancer in the Asian pacific-epidemiology, screening and treatment. *Asian Pac J Cancer Prev* 2003;5:349–361.
- Ferlay J, Soerjomataram I, Ervik M, et al. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11*. Lyon, France: International Agency for Research on Cancer [Internet]. 2013 Available: <http://globocan.iarc.fr> (17 August 2014, date last accessed).
- Shah KV. Asia Pacific: cervical cancer screening and human papillomavirus vaccination policy and delivery. *Vaccine* 2008;26. doi:10.1016/j.vaccine.2008.06.033.
- Orth G, Jablonska S, Jarzabek-Chorzelska M, et al. Characteristics of the lesions and risk of malignant conversion associated with the type of human papillomavirus involved in epidermodysplasia verruciformis. *Cancer Res* 1979;39:1074–1082.
- zur Hausen H. Papillomaviruses in anogenital cancer as a model to understand the role of viruses in human cancers. *Cancer Res* 1989;49:4677–4681.
- Bruni L, Diaz M, Castellsagué M, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis* 2010; 202:1789–1799. doi:10.1086/657321.
- Burd E. Human papillomavirus and cervical cancer. *Clin Microbiol Rev* 2003;16:1–17. doi:10.1128/CMR.16.1.1.
- Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015;107:djv086 doi:10.1093/jnci/djv086.
- Bonanni P, Bechini A, Donato R, et al. Human papilloma virus vaccination: impact and recommendations across the world. *Ther Adv Vaccines* 2014;3:3–12. doi:10.1177/2051013614557476.
- Indications CERVARIX® is indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18 [see Clinical Studies (14)]: • cervical cancer, • cervical intraepithelial neoplasia (CIN) grade 2 or w. 2009; 1–27.
- Girls and Women GARDASIL® is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine: Genital warts (condyloma acuminata) caused. 2006;
- index @ www.gardasil.com [Internet]. Available: <http://www.gardasil.com/>
- Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus 1618 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374:301–14.
- The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356: 1915–27.
- Malagón T, Drolet M, Boily M-C, Franco EL, Jit M, Brisson J, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12:781–9. doi:10.1016/S1473-3099(12)70187-1.
- Dillner J, Kjaer SK, Wheeler CM, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. *BMJ* 2010;341:c3493. doi:10.1136/bmj.c3493.

17. Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine. *Hum Vaccin Immunother* 2014;10:2147–2162. doi:10.4161/hv.29532.
18. Schwarz TF, Huang L-M, Lin T-Y, et al. Long-term immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in 10- to 14-year-old girls. *Pediatr Infect Dis J* 2014;33:1255–1261. doi:10.1097/INF.0000000000000460.
19. Hallez S, Simon P, Maudoux F, et al. Phase I/II trial of immunogenicity of a human papillomavirus (HPV) type 16 E7 protein-based vaccine in women with oncogenic HPV-positive cervical intraepithelial neoplasia. *Cancer Immunol Immunother* 2004;53:642–650. doi:10.1007/s00262-004-0501-4.
20. Giuliano AR, Lazcano-Ponce E, Villa L, et al. Impact of baseline covariates on the immunogenicity of a quadrivalent (types 6, 11, 16, and 18) human papillomavirus virus-like-particle vaccine. *J Infect Dis* 2007;196:1153–1162. doi:10.1086/521679.
21. Wheeler CM, Bautista OM, Tomassini JE, Nelson M, Sattler CA, Barr E. Safety and immunogenicity of co-administered quadrivalent human papillomavirus (HPV)-6/11/16/18 L1 virus-like particle (VLP) and hepatitis B (HBV) vaccines. *Vaccine* 2008;26:686–696. doi:10.1016/j.vaccine.2007.11.043.
22. Eriksson T, Torvinen S, Woodhall SC, et al. Impact of HPV16/18 vaccination on quality of life: a pilot study. *Eur J Contracept Reprod Heal care* 2013;18:364–71. doi:10.3109/13625187.2013.801953.
23. Pondo T, Rose CE, Martin SW, et al. Evaluation of sex, race, body mass index and pre-vaccination serum progesterone levels and post-vaccination serum anti-anthrax protective immunoglobulin G on injection site adverse events following anthrax vaccine adsorbed (AVA) in the CDC AVA human clinical. *Vaccine* 2014;32:3548–54. doi:10.1016/j.vaccine.2014.04.025.
24. Jiang V, Jiang B, Tate J, Parashar UD, Patel MM. Performance of rotavirus vaccines in developed and developing countries. *Hum Vaccin* 2010;6:532–542. doi:10.4161/hv.6.7.11278.
25. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Reprinted from Annals of Internal Medicine). *Phys Ther* 2009;89:873–880. doi:10.1371/journal.pmed.1000097.
26. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928–d5928. doi:10.1136/bmj.d5928.
27. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw* 2010;36:1–48. doi:10.1103/PhysRevB.91.121108.
28. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
29. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 2011. Available: http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm
30. Kang S, Kim KH, Kim YT, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects. *Int J Gynecol Cancer* 2008;18:1013–1019. doi:10.1111/j.1525-1438.2007.01123.x.
31. Konno R, Dobbelaere KO, Godeaux OO, Tamura S, Yoshikawa H. Immunogenicity, reactogenicity, and safety of human papillomavirus 16/18 AS04-adjuvanted vaccine in Japanese women: interim analysis of a phase II, double-blind, randomized controlled trial at month 7. *Int J Gynecol Cancer* 2009;19:905–911. doi:10.1111/IGC.0b013e3181a23c0e.
32. Kim YJ, Kim KT, Kim JH, et al. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10–14 years. *J Korean Med Sci* 2010;25:1197–1204. doi:10.3346/jkms.2010.25.8.1197.
33. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. *J Obstet Gynaecol Res* 2010;36:123–132. doi:10.1111/j.1447-0756.2009.01167.x.
34. Ngan HYS, Cheung ANY, Tam KF, et al. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: Immunogenicity and safety in healthy Chinese women from Hong Kong. *Hong Kong Med J* 2010;16:171–179.
35. Kim SC, Song YS, Kim YT, et al. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: Immunogenicity and safety in 15–25 years old healthy Korean women. *J Gynecol Oncol* 2011;22:67–75. doi:10.3802/jgo.2011.22.2.67.
36. Khatun S, Akram Hussain SM, Chowdhury S, et al. Safety and immunogenicity profile of human papillomavirus-16/18 as04 adjuvant cervical cancer vaccine: a randomized controlled trial in healthy adolescent girls of Bangladesh. *Jpn J Clin Oncol* 2012;42:36–41. doi:10.1093/jjco/hyr173.
37. Li R, Li Y, Radley D, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: A randomized, double-blind, placebo-controlled trial in Chinese males and females. *Vaccine* 2012;30:4284–4291. doi:10.1016/j.vaccine.2012.02.079.
38. Lim BK, Ng KY, Omar J, et al. Immunogenicity and safety of the AS04-adjuvanted human papillomavirus-16/18 cervical cancer vaccine in Malaysian women aged 18–35 years: a randomized controlled trial. *Med J Malaysia* 2014;69:2–8.
39. Zhu F-C, Chen W, et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18–25 years: results from a randomised controlled trial. *Int J Cancer* 2014;2622:2612–2622. doi:10.1002/ijc.28897.
40. Perez G, Lazcano-Ponce E, Hernandez-Avila M, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women. *Int J Cancer* 2008;122:1311–1318. doi:10.1002/ijc.23260.
41. Block SL, Nolan T, Sattler C, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics* 2006;118:2135–2145. doi:10.1542/peds.2006-0461.
42. Einstein MH, Takacs P, Chatterjee A, et al. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18–45 years: End-of-study analysis of a Phase III randomized trial. *Hum Vaccin Immunother* 2015;10:3435–3445. doi:10.4161/hv.36121.
43. Muñoz N, Manalastas R, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. *Lancet* 2009;373:1949–1957. doi:10.1016/S0140-6736(09)60691-7.
44. Sow PS, Watson-Jones D, Kiviat N, et al. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: a randomized trial in 10–25-year-old HIV-Seronegative African girls and young women. *J Infect Dis* 2013;207:1753–63. doi:10.1093/infdis/jis619.
45. Kreimer R, Schiffman M, Herrero R, et al. Long-term risk of recurrent cervical human papillomavirus infection and precancer and cancer following excisional treatment. *Int J Cancer* 2012;doi:10.1002/ijc.26349.
46. Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. *BMC Infect Dis* 2011;11:13. doi:10.1186/1471-2334-11-13.
47. Davies W India Has Most Cervical Cancer Deaths [Internet]. 2013 Available: <http://blogs.wsj.com/indiarealtime/2013/05/10/india-has-highest-number-of-cervical-cancer-deaths/> (30 December 2014, date last accessed)
48. Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. *Int J Womens Health* 2015;7:405–14. doi:10.2147/IJWH.S50001.
49. Siddaway A. What is a systematic literature review and how do I do one? Univ Stirling. 2014; 1–13. Available: <https://www.stir.ac.uk/media/schools/management/documents/centregradresearch/How to do a systematic literature review and meta-analysis.pdf>
50. Lee A, Done M. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. *Anesth Analg* 2004;99:1870. doi:10.1002/14651858.CD003110.7.
51. Shuster JJ, Walker MA. Low-event-rate meta-analyses of clinical trials: Implementing good practices. *Stat Med* 2016;35:2467–2478. doi:10.1002/sim.6844.

52. Setiawan D, Luttjeboer J, Westra TA, et al. The cost-effectiveness of HPV vaccination in addition to screening: a Dutch perspective. *Expert Rev Vaccines* 2015;14:589–604. doi:10.1586/14760584.2014.990386.
53. Burger E a, Sy S, Nygård M, Kristiansen IS, Kim JJ. Prevention of HPV-related cancers in Norway: cost-effectiveness of expanding the HPV vaccination program to include pre-adolescent boys. *PLoS One* 2014;9: e89974 doi:10.1371/journal.pone.0089974.
54. Ferris D, Samakoses R, Block SL, et al. Long-term study of a quadrivalent human papillomavirus vaccine. *Pediatrics* 2014;134:e657–e665. doi:10.1542/peds.2013-4144.
55. Rey-Ares L, Ciapponi A, Pichon-Riviere A. Efficacy and safety of human papilloma virus vaccine in cervical cancer prevention: systematic review and meta-analysis. *Arch Argent Pediatr* 2012;110:483–9. doi:10.1590/S0325-00752012000600005.
56. Suwantika AA, Postma MJ. Expanding access to non-traditional vaccines: a perspective from Indonesia Expanding access to non-traditional vaccines: a perspective from Indonesia. 2016;584 doi:10.1586/14760584.2014.944165.
57. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. *Lancet Glob Heal* 2014;2:e406–14. doi:10.1016/S2214-109X(14)70237-2.
58. Wong MCS, Lee A, Ngai KKL, Chor JCY, Chan PKS. Knowledge, attitude, practice and barriers on vaccination against human papillomavirus infection: a cross-sectional study among primary care physicians in Hong Kong. *PLoS One* 2013;8:1–10. doi:10.1371/journal.pone.0071827.
59. Graham JE, Mishra A. Global challenges of implementing human papillomavirus vaccines. *Int J Equity Health* 2011;10:27 doi:10.1186/1475-9276-10-27.
60. Wigle J, Coast E, Watson-jones D. Human papillomavirus (HPV) vaccine implementation in low and middle-income countries (LMICs): Health system experiences and prospects. *Vaccine* 2013;31:3811–3817. doi:10.1016/j.vaccine.2013.06.016.
61. Guerra FA. Delays in immunization have potentially serious health consequences. 2007;9:143–148.
62. Gefenaitte G, Smit M, Nijman HW, et al. Comparatively low attendance during Human Papillomavirus catch-up vaccination among teenage girls in the Netherlands: insights from a behavioral survey among parents. *BMC Public Health* 2012;12:498 doi:10.1186/1471-2458-12-498.
63. Kim Y-M, Lambe FM, Soetikno D, et al. Evaluation of a 5-year cervical cancer prevention project in Indonesia: opportunities, issues, and challenges. *J Obstet Gynaecol Res* 2013;39:1190–9. doi:10.1111/jog.12052.
64. Connolly MP, Topachevskyi O, Standaert B, Ortega O, Postma M. The impact of rotavirus vaccination on discounted net tax revenue in Egypt: a government perspective analysis. *Pharmacoeconomics* 2012;30:681–695. doi:10.2165/11597750.
65. Sachs JD. Macroeconomics and Health: Investing in Health for Economic Development [Internet]. Geneva; 2001 Jun. doi:10.1038/nm0602-551b
66. Nelson R. EU Recommends Approval of Gardasil 9 Vaccine [Internet]. 2015 Available: http://www.medscape.com/viewarticle/562858_print (20 April 2015, date last accessed)
67. Sankaranarayanan R, Prabhu PR, Pawlita M, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. *Lancet Oncol* 2016;17:67–77. doi:10.1016/S1470-2045(15)00414-3.
68. Kreimer AR, Struyf F, Wacholder S, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. *Lancet Oncol* 2015;16:775–86. doi:10.1016/S1470-2045(15)00047-9.